Tetrahedron Letters 55 (2014) 1255–1257

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of an azabicyclic framework towards (±)-actinophyllic acid ☆

Danny Mortimer [a], Matthew Whiting [b], Joseph P. A. Harrity [a,*], Simon Jones [a,*], Iain Coldham [a,*]

[a] Department of Chemistry, University of Sheffield, Brook Hill, Sheffield S3 7HF, UK
[b] GlaxoSmithKline Research and Development, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY, UK

ARTICLE INFO

Article history:
Received 16 October 2013
Revised 6 December 2013
Accepted 6 January 2014
Available online 10 January 2014

Keywords:
Mannich
Indole
Actinophyllic acid
1-Azabicyclo[4.2.1]nonane
Azocinone

ABSTRACT

Lewis acid mediated intramolecular Mannich reaction between an azocinone and a 3-formylindole was investigated as part of a study towards the synthesis of actinophyllic acid. The intramolecular Mannich reaction resulted in a single diastereomer of the 1-azabicyclo[4.2.1]nonan-5-one core framework, although single crystal X-ray structure analysis revealed that this had the undesired stereochemistry in comparison with the natural product.

Many monoterpene indole alkaloids from the secologanin biosynthetic route have been discovered,[1] including the novel indole alkaloid actinophyllic acid (**1**) (Fig. 1), which was isolated from the leaves of *Alstonia actinophylla* (Apocynaceae).[2] This bioactive alkaloid was isolated using a bioassay-guided fractionation of the aqueous phase employing a CPU/hippuricase coupled enzyme assay to detect carboxypeptidase U inhibitors. Actinophyllic acid was found to be a potent inhibitor of this enzyme assay with an IC_{50} of 0.84 μM. Inhibition of carboxypeptidase U may facilitate fibrinolysis (the process by which the body removes small blood clots from circulation) and, therefore, has the potential to act as a treatment for cardiovascular disorders.[2] The structure of actinophyllic acid (**1**) contains a complex fused alkaloid ring system containing an azabicycle **2** bridged to an indole.

The first total synthesis of actinophyllic acid was achieved by Overman and co-workers.[3] The key synthetic step employed an aza-Cope Mannich reaction to achieve the desired framework. Optical rotation and electronic circular dichroism measurements on the separated methyl ester enantiomers allowed the absolute configuration to be assigned.[4] Overman and co-workers also reported the first enantioselective total synthesis as well as improvements to the end game strategy.[5] Martin and co-workers have recently reported an alternative total synthesis which includes structural analogues.[6] Other routes towards the synthesis of actinophyllic acid (**1**) have also been reported.[7]

The Mannich reaction is historically useful for the synthesis of alkaloid frameworks.[8] With Overman's route in mind, an alternative approach to the 1-azabicyclo[4.2.1]nonan-5-one core **2** was envisaged employing an intramolecular Mannich reaction. Recently, Maldonado and co-workers reported a similar strategy employing a Mannich reaction to give the azabicyclic core ring system.[7c] We herein report our results as a comparable approach.

The first step in the retrosynthetic strategy disconnects the hemi-acetal providing the malonoyl indole **3** (Fig. 2). The forward sense of this retrosynthetic disconnection was clarified by Overman and co-workers.[3] This known malonoyl indole **3** contains a 1,4-dicarbonyl, and could be disconnected to the azabicyclo[4.2.1]nonan-5-one **4**. The key step towards this ring system

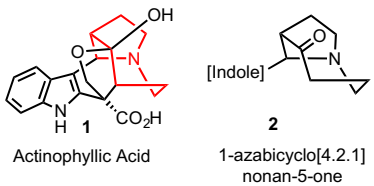


Figure 1. Actinophyllic acid (**1**) and azabicyclic core **2**.

* Corresponding authors. Tel.: +44 114 222 9496; fax: +44 114 222 9346.
E-mail addresses: j.harrity@shef.ac.uk (J.P.A. Harrity), simon.jones@shef.ac.uk (S. Jones), i.coldham@shef.ac.uk (I. Coldham).

0040-4039/$ - see front matter © 2014 The Authors. Published by Elsevier Ltd. All rights reserved.

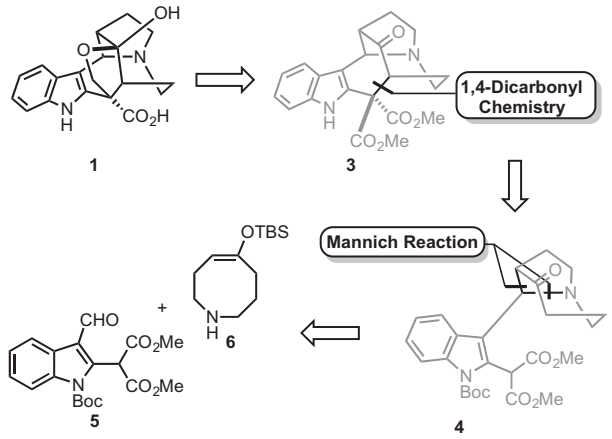


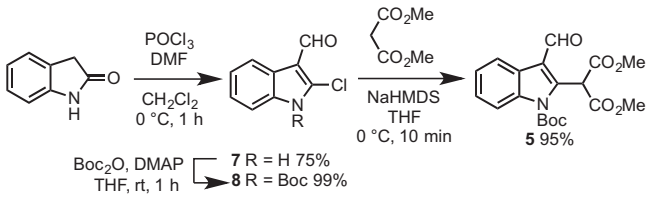
Figure 2. Retrosynthetic analysis.

would then be to employ an intramolecular Mannich reaction between the 3-formylindole **5** and the 8-membered ring amine **6**.

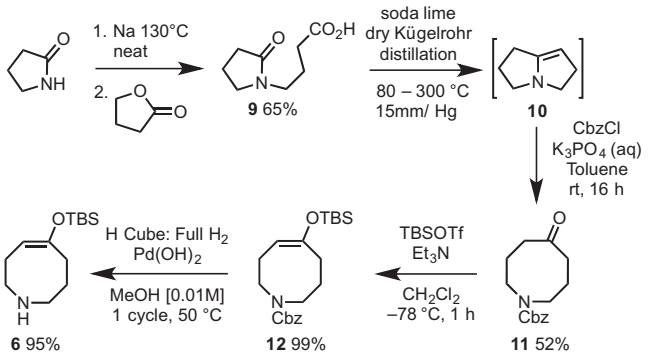
The synthesis of the indole **5** started with the known transformation of oxindole to 2-chloro-3-formylindole (**7**) using Vilsmeier's reagent.[9] Subsequent nitrogen protection with Boc_2O gave the indole **8** in excellent yield. Deprotonation of dimethyl malonate with NaHMDS in THF at 0 °C and treatment with indole **8** pleasingly gave the desired indole **5** in 95% yield (see Scheme 1).

The eight-membered azocan-5-one (azocinone) ring was constructed by optimising the work of Miyano.[10] Following the reported procedure, neat pyrrolidinone was treated with elemental sodium at 130 °C, and then subsequently with γ-butyrolactone which gave carboxylic acid **9** in 65% yield.[10a] This was then distilled from finely ground soda lime.[10a–c] It was found that this reaction achieved the highest yield when the reaction was performed in a Kügelrohr distillation apparatus with a bulb-to-bulb distillation, yielding pure tetrahydropyrrolizine **10** that was immediately treated with CbzCl in biphasic aqueous 30% K_3PO_4 and toluene (rather than via the reported hexahydropyrrolizinium perchlorate salt)[10d,10e] to generate the *N*-Cbz azocinone **11** in a modest yield from carboxylic acid **9**.[10f,g] The required TBS enol ether **12** was prepared from the *N*-Cbz azocinone **11** by treatment with TBSOTf and Et_3N at low temperature in excellent yield. Finally, cleaving the *N*-Cbz protecting group, by subjecting *O*-TBS enol ether **12** to hydrogenolysis using the H-Cube™ with $Pd(OH)_2/C$ CatCart™, provided amine **6** in excellent yield (see Scheme 2).

The Mannich reaction was initially attempted with Brønsted acids ([0.1–6 M] HCl, TsOH) in protic (H_2O, MeOH) or aprotic (Et_2O, toluene, THF) solvents. However, this led to recovery of indole **5** and decomposition of amine **6** to tetrahydropyrrolizine **10**. To prevent the formation of tetrahydropyrrolizine **10**, milder reaction conditions were investigated. There are reports of Lewis acid mediated Mannich reactions,[11] and the use of silyl enol ethers as reagents.[8,12] Efforts towards accessing azabicycle **4** were conducted with a Lewis acid that could promote iminium ion formation, but was not so strong that it would deprotect the silyl enol

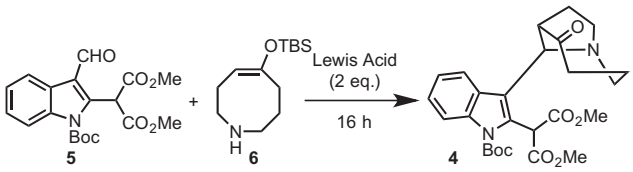


Scheme 1. Synthesis of indole malonate **5**.



Scheme 2. Synthesis of amine **6**.

Table 1
Lewis acid screen



Entry	Lewis acid	Solvent	Temp (°C)	**4** (%)
1	$B(C_6F_5)_3$	CH_2Cl_2	rt	0
2	BPh_3	CH_2Cl_2	rt	8
3	$B(OMe)_3$	CH_2Cl_2	rt	0
4	$AuCl_3$	CH_2Cl_2	rt	0
5	$Ti(O^iPr)_4$	CH_2Cl_2	rt	1
6	$Zn(BF_4)_2$	CH_2Cl_2	rt	2
7	$MgBr_2{\cdot}OEt_2$	CH_2Cl_2	rt	9
8	AgOAc	CH_2Cl_2	rt	0
9	BPh_3	CH_2Cl_2	40	20
10	BPh_3	1,2-Dichloroethane	40	14
11	BPh_3	$PhCF_3$	40	30
12	BPh_3	$PhCF_3/H_2O$ (9:1)	40	40

ether. Amine **6** and aldehyde **5** were treated with a range of Lewis acids (2 equiv) at room temperature for 16 h, giving the desired azabicycle **4** with mixed results (Table 1).

Lewis acids $B(C_6F_5)_3$, $B(OMe)_3$,[11a] $AuCl_3$[11b] and AgOAc[11c] failed to produce any of the desired product (entries 1, 3, 4 and 8, respectively). However, the desired amine **4** was obtained in 8%, 1%, 2% and 9% yield using BPh_3,[11d] $Ti(O^iPr)_4$, $Zn(BF_4)_2$[11e] and $MgBr_2{\cdot}OEt_2$,[11f] respectively (entries 2, 5–7). Elevating the temperature to 40 °C, when employing BPh_3, increased the yield from 8% to 20% (entry 9).[13] Changing the solvent to 1,2-dichloroethane failed to improve the reaction (entry 10). Interestingly, changing to trifluorotoluene improved the yield to 30% (entry 11), with the addition of trace quantities of water improving the yield further (entry 12).[14]

Azabicycle **4** was isolated as a single diastereomer with the molecular structure being confirmed by HSQC and ROSEY 2D NMR experiments. The relative stereochemistry was confirmed as *anti* by single crystal X-ray analysis. This is different from that required for the synthesis of actinophyllic acid.[15] The X-ray crystal structure shows a hydrogen bonding interaction between the amine and the C–H of the malonate. Maldonado and co-workers also reported *anti* selectivity (see Fig. 3).[7c]

The cyclisation is likely to occur by nucleophilic attack of the silyl enol ether onto the indole **13** (or possibly the iminium ion).

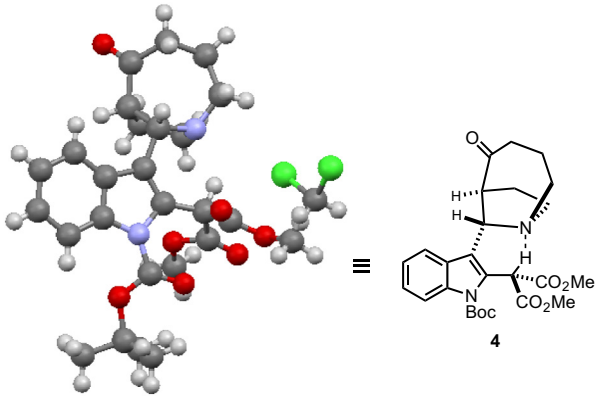


Figure 3. X-ray crystal structure (ORTEP) of **4**.

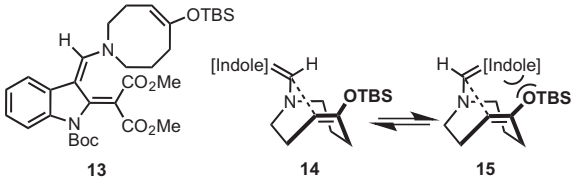


Figure 4. Possible diastereoselectivity rationale.

The diastereoselectivity must arise either from a thermodynamic preference for the isomer **4**, or from a preference for a transition state of general structure **14** rather than **15**. The latter has a steric clash between the indole unit and the OTBS group (see Fig. 4).

In conclusion, the synthesis of the azabicycle **4** core system with *anti* diastereoselectivity was achieved using a BPh_3-mediated intramolecular Mannich reaction. Current investigations are underway using an approach in which the 1,4-dicarbonyl functionality is set up prior to the transannular Mannich reaction.

Acknowledgments

We would like to thank GSK and EPSRC for funding and Harry Adams for the X-ray crystallographic analysis.

References and notes

1. Ishikura, M.; Yamada, K.; Abe, T. *Nat. Prod. Rep.* **2010**, *27*, 1630–1680.
2. Carroll, A. R.; Hyde, E.; Smith, J.; Quinn, R. J.; Guymer, G.; Forster, P. I. *J. Org. Chem.* **2005**, *70*, 1096–1099.
3. Martin, C. L.; Overman, L. E.; Rohde, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 7568–7569.
4. Taniguchi, T.; Martin, C. L.; Monde, K.; Nakanishi, K.; Berova, N.; Overman, L. E. *J. Nat. Prod.* **2009**, *72*, 430–432.
5. Martin, C. L.; Overman, L. E.; Rohde, J. M. *J. Am. Chem. Soc.* **2010**, *132*, 4894–4906.
6. Butler, J. D.; Hua, B.; Knezevic, C. E.; Parkinson, E. I.; Hergenrother, P. J.; Martin, S. F. *J. Am. Chem. Soc.* **2013**, *135*, 12984–12986.
7. (a) Vaswani, R. G.; Day, J. J.; Wood, J. L. *Org. Lett.* **2009**, *11*, 4532–4535; (b) Zaimoku, H.; Taniguchi, T.; Ishibashi, H. *Org. Lett.* **2012**, *14*, 1656–1658; (c) Galicia, I. Z.; Maldonado, L. A. *Tetrahedron Lett.* **2013**, *54*, 2180–2182.
8. Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044–1070.
9. Pedras, M. S. C.; Suchy, M.; Ahiahonu, P. W. K. *Org. Biomol. Chem.* **2006**, *4*, 691–701.
10. (a) Miyano, S.; Fujii, S.; Yamashita, O.; Toraishi, N.; Sumoto, K. *J. Heterocycl. Chem.* **1982**, *19*, 1465–1468; (b) Sumoto, K.; Fujii, S.; Yamashita, O.; Somehara, T.; Miyano, S. *J. Heterocycl. Chem.* **1981**, *18*, 413–414; (c) Miyano, S.; Sumoto, K.; Satoh, F.; Shima, K.; Hayashimatsu, M.; Morita, M.; Aisaka, K.; Noguchi, T. *J. Med. Chem.* **1985**, *28*, 714–717; (d) Miyano, S.; Somehara, T.; Nakao, M.; Sumoto, K. *Synthesis* **1978**, 701–702; (e) Miyano, S.; Mibu, N.; Fujii, S.; Abe, N.; Sumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2611–2613; (f) Sumoto, K.; Mibu, N.; Irie, M.; Abe, N.; Miyano, S. *Chem. Pharm. Bull.* **1990**, *38*, 577–580; (g) Miyano, S.; Mibu, N.; Irie, M.; Sumoto, K. *Heterocycles* **1986**, *24*, 2121–2125.
11. (a) Tanaka, Y.; Hidaka, K.; Hasui, T.; Suginome, M. *Eur. J. Org. Chem.* **2009**, 1148–1151; (b) Xu, L. W.; Xia, C. G.; Li, L. *J. Org. Chem.* **2004**, *69*, 8482–8484; (c) Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 3734–3735; (d) Tanaka, Y.; Hasui, T.; Suginome, M. *Synlett* **2008**, 1239–1242; (e) Badorrey, R.; Cativiela, C.; Diaz-de-Villegas, M. D.; Galvez, J. A. *Tetrahedron Lett.* **2003**, *44*, 9189–9192; (f) Hatano, M.; Horibe, T.; Ishihara, K. *Org. Lett.* **2010**, *12*, 3502–3505.
12. (a) Kobayashi, S.; Ishitani, H.; Komiyama, S.; Oniciu, D. C.; Katritzky, A. R. *Tetrahedron Lett.* **1996**, *37*, 3731–3734; (b) Danishefsky, S.; Kahn, M.; Silvestri, M. *Tetrahedron Lett.* **1982**, *23*, 1419–1422.
13. Boranes have been reported to promote iminium ion formation, see: (a) Suginome, M.; Uehlin, L.; Murakami, M. *J. Am. Chem. Soc.* **2004**, *126*, 13196–13197; (b) Suginome, M. *Pure Appl. Chem.* **2006**, *78*, 1377–1387.
14. *Synthesis of* ***4****:* BPh_3 (100 mg) was added in one portion to a stirred solution of aldehyde **5** (78 mg, 0.21 mmol) and amine **6** (50 mg, 0.21 mmol) in trifluorotoluene (4 mL) at 40 °C under nitrogen. After 16 h, the reaction mixture was combined with H_2O (5 mL) and CH_2Cl_2 (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated. Purification by column chromatography on silica, eluting with petrol–EtOAc (1:1) gave indole **4** (40 mg, 40%) as needles; mp 177–178 °C; R_f [petrol–EtOAc (1:1)] 0.1; IR ν_{max}/cm^{-1} 3050, 2930, 1740, 1690, 1640, 1440; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.96 (d, *J* = 8.0 Hz, 1H, Ar), 7.60 (s, 1H, CH), 7.33 (d, *J* = 8.0 Hz, 1H, Ar), 7.23 (t, *J* = 8.0 Hz, 1H, Ar), 7.15 (t, *J* = 8.0 Hz, 1H, Ar), 4.97 (s, 1H, CH), 3.65 (s, 3H, CH_3), 3.62 (s, 3H, CH_3), 3.48 (d, *J* = 8.5 Hz, 1H, CH), 3.12–2.99 (m, 3H, CH_2 + CH_AH_B), 2.93–2.87 (m, 1H, CH_AH_B), 2.81 (td, *J* = 16.0, 2.5 Hz, 1H, CH_AH_B), 2.58 (dd, *J* = 16.0, 5.0 Hz, 1H, CH_AH_B), 2.08–1.95 (m, 3H, CH_2 + CH_AH_B), 1.66–1.62 (m, 1H, CH_AH_B), 1.56 (s, 9H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 213.4 (CO), 167.9 (CO), 167.5 (CO), 150.6 (CO), 135.6 (C), 129.1 (C), 127.8 (C), 124.5 (CH), 122.5 (CH), 119.5 (CH), 117.8 (C), 116.0 (CH), 84.5 (C), 66.3 (CH), 60.1 (CH), 57.2 (CH_2), 52.5 (CH_3), 52.4 (CH_3), 50.2 (CH_2), 47.7 (CH), 41.7 (CH_2), 31.3 (CH_2), 28.1 (CH_3), 23.7 (CH_2); MS (ESI) *m*/*z* 485 [$(M+H)^+$ 100]; HRMS (ESI) calcd for $C_{26}H_{33}N_2O_7$ $(M+H)^+$ 485.2288 found 485.2295.
15. Crystallographic data (excluding structure factors) for the structure in this Letter has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 949237. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).